

Figure 3: *In vivo* Effect on Blood Glucose with Crosslinked PDA-PVAm Copolymers after 4 Weeks of Treatment

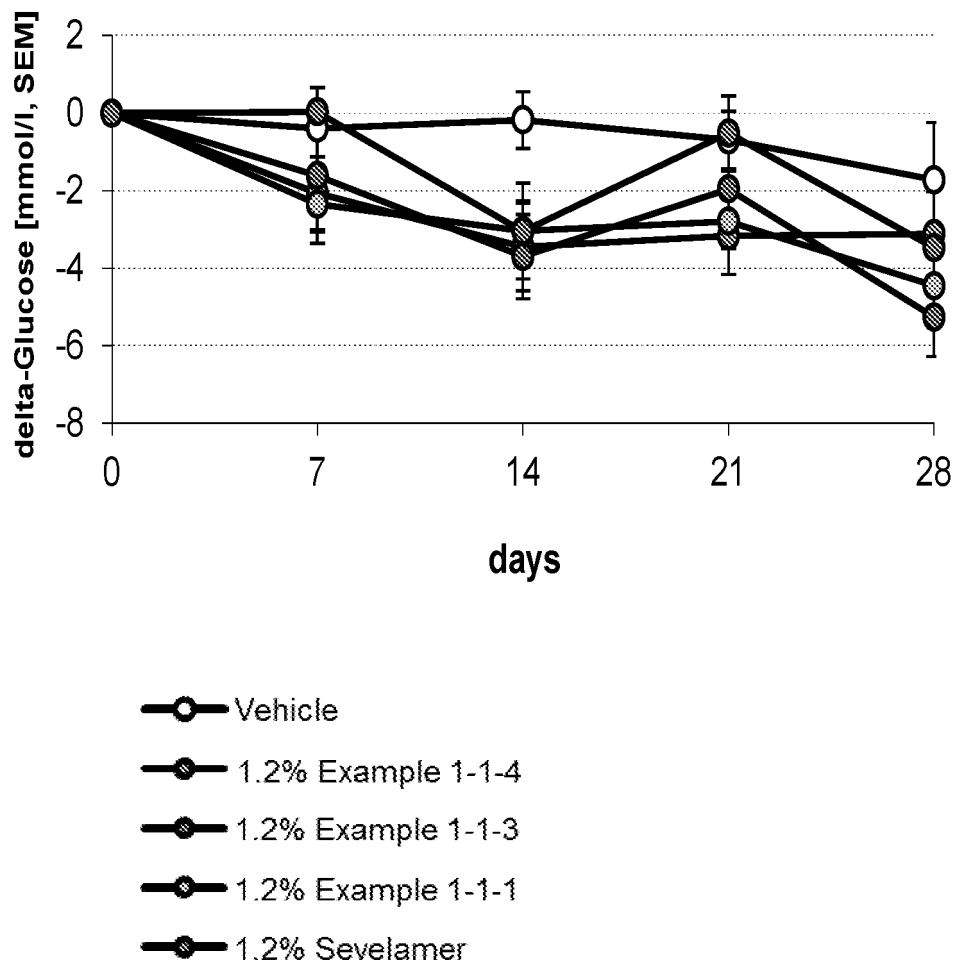


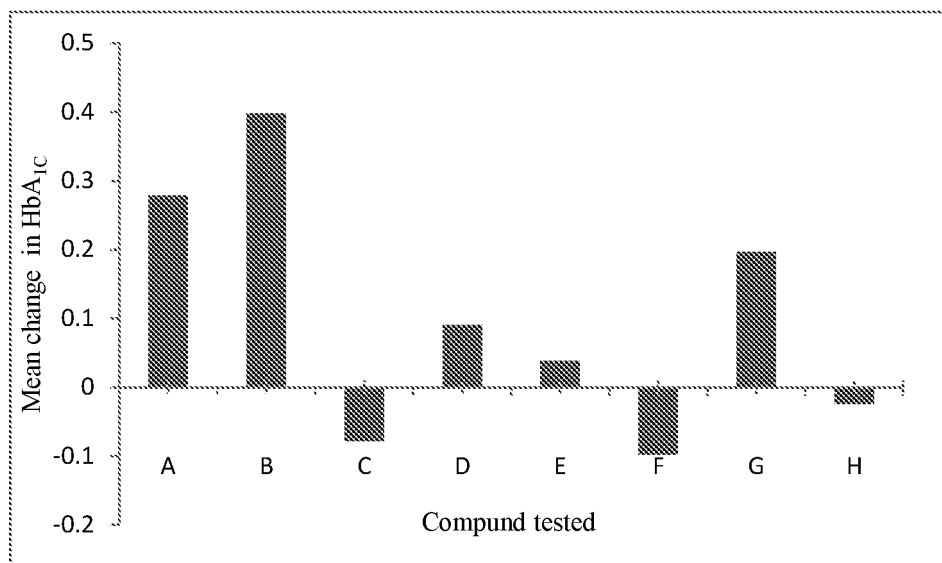
Table 8: *In vivo* Effect on Plasma Insulin with Crosslinked PDA-PVAm Copolymers

Test Article	Dose (% of diet)	Non-fasted blood glucose normalized to start date (Δ glucose, mmol/L)		
		Week 2	Week 3	Week 4
Control	0	--	--	-1.7
Example 1- 1- 4	1.2	--	--	-1.5

Example 1- 1- 3	1.2	--	--	-1.9
Example 1- 1- 1	1.2	--	--	-4.6
Sevelamer	1.2	--	--	-3.8

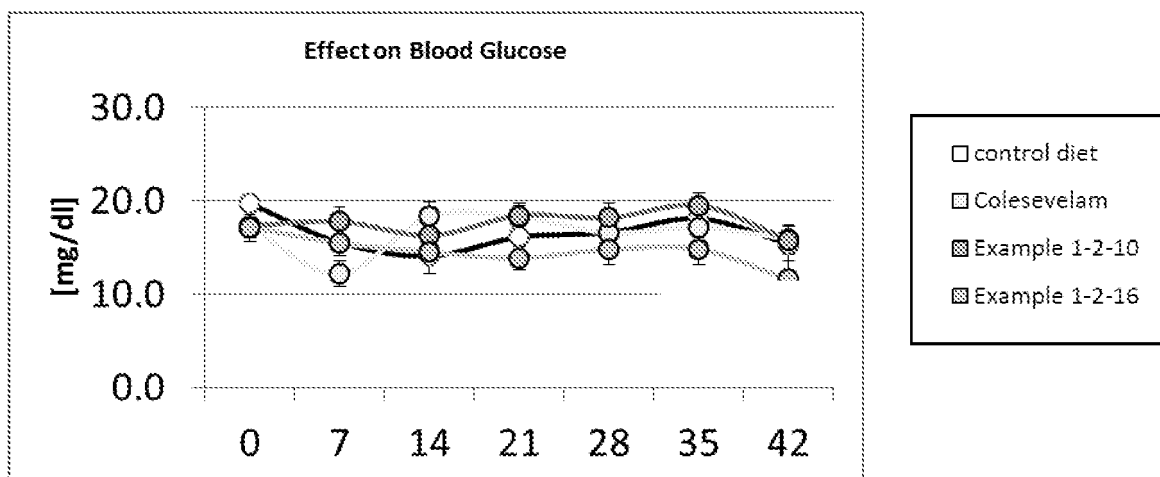
-- indicates not tested

Figure 4: *In vivo* Effect on HbA_{1c} with Crosslinked PDA-PVAm Copolymers after 4 Weeks of Treatment



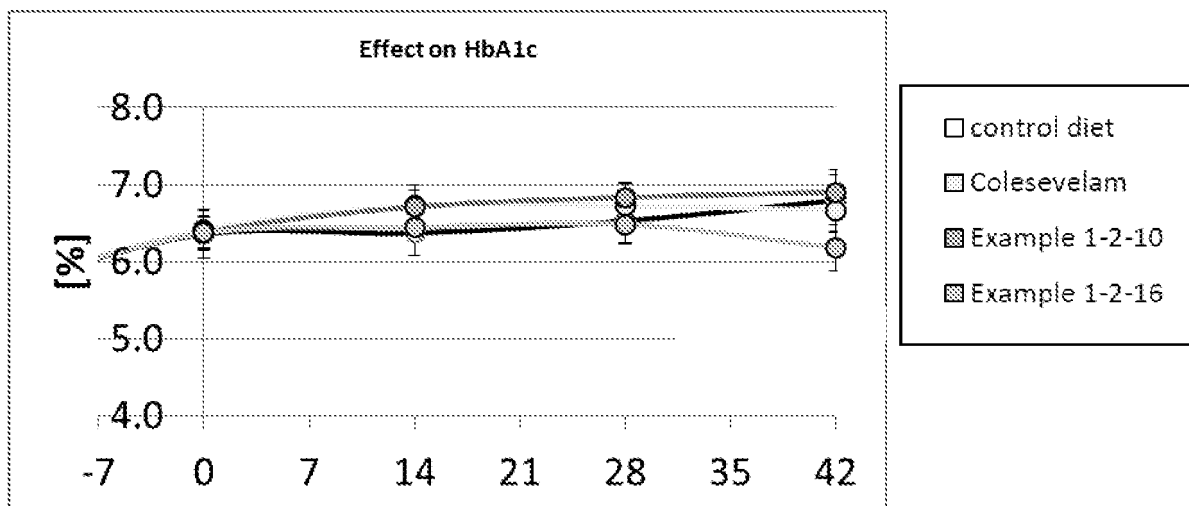
A = vehicle control; B = sevelamer; C = linagliptin; D = Example 1- 1- 4; E = Example 1- 1- 3;
F = Example 1- 1- 1; G = sevelamer + linagliptin; H = Example 1- 1- 3 + linagliptin

Figure 5: *In vivo* Effect on Blood Glucose with Crosslinked PDA-PAA Copolymers



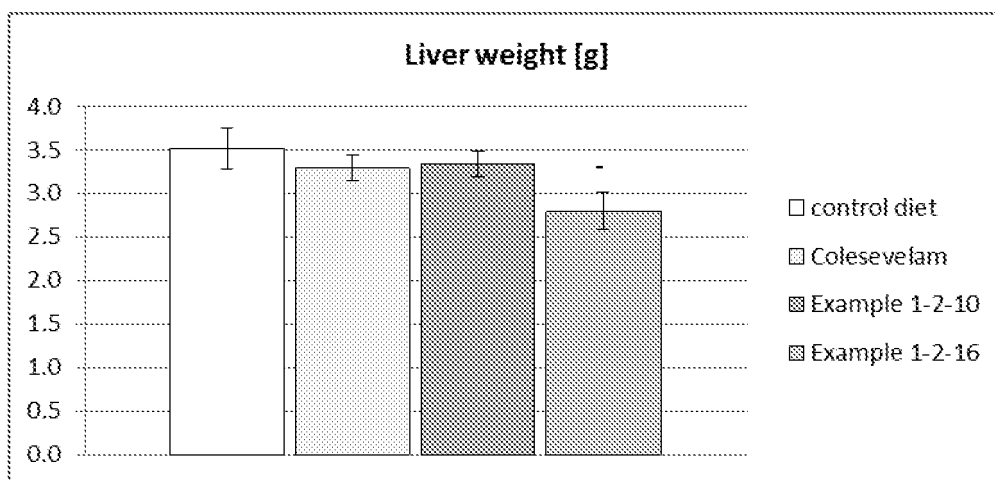
The *in vivo* effect of different compositions of crosslinked PDA-PAA copolymers on blood glucose of dbd/db mice with escalating dose of test articles are presented in Figure 5. The animals were given increased dose of the compounds at two-week intervals (1 wt.% (day 0), 2 wt.% (day 14) and 3 wt.% (day 28) of diet).

Figure 6: *In vivo* Effect on HbA1c with Crosslinked PDA-PAA Copolymers



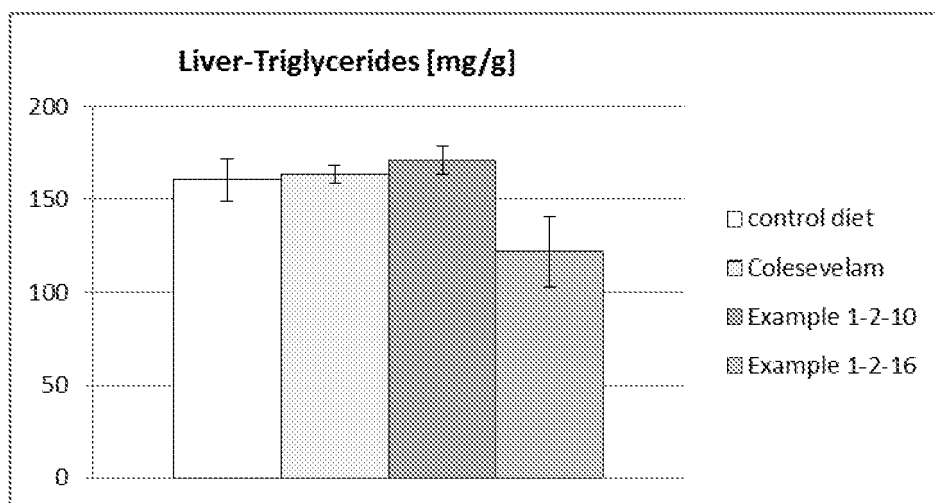
The *in vivo* effect of different compositions of crosslinked PDA-PAA copolymers on blood HBA1C of dbd/db mice with escalating dose of test articles are presented in Figure 6. The animals were given increased dose of the compounds at two-week intervals (1 wt.% (day 0), 2 wt.% (day 14) and 3 wt.% (day 28) of diet).

Figure 7: *In vivo* Effect on Liver Weight with Crosslinked PDA-PAA Copolymers



The *in vivo* effect of different compositions of crosslinked PDA-PAA copolymers on liver weight of dbd/db mice with escalating dose of test articles are presented in Figure 7. The animals were given increased dose of the compounds at two-week intervals (1 wt.% (day 0), 2 wt.% (day 14) and 3 wt.% (day 28) of diet).

Figure 8: *In vivo* Effect on Liver Triglycerides with Crosslinked PDA-PAA Copolymers



The *in vivo* effect of different compositions of crosslinked PDA-PAA copolymers on liver triglyceride contents of dbd/db mice with escalating dose of test articles are presented in Figure 8. The animals were given increased dose of the compounds at two-week intervals (1 wt.% (day 0), 2 wt.% (day 14) and 3 wt.% (day 28) of diet).

Example 3- 3: *In vivo* Effect of Crosslinked PDA-PVAm and PDA-PAA Copolymers on Insulin Resistance

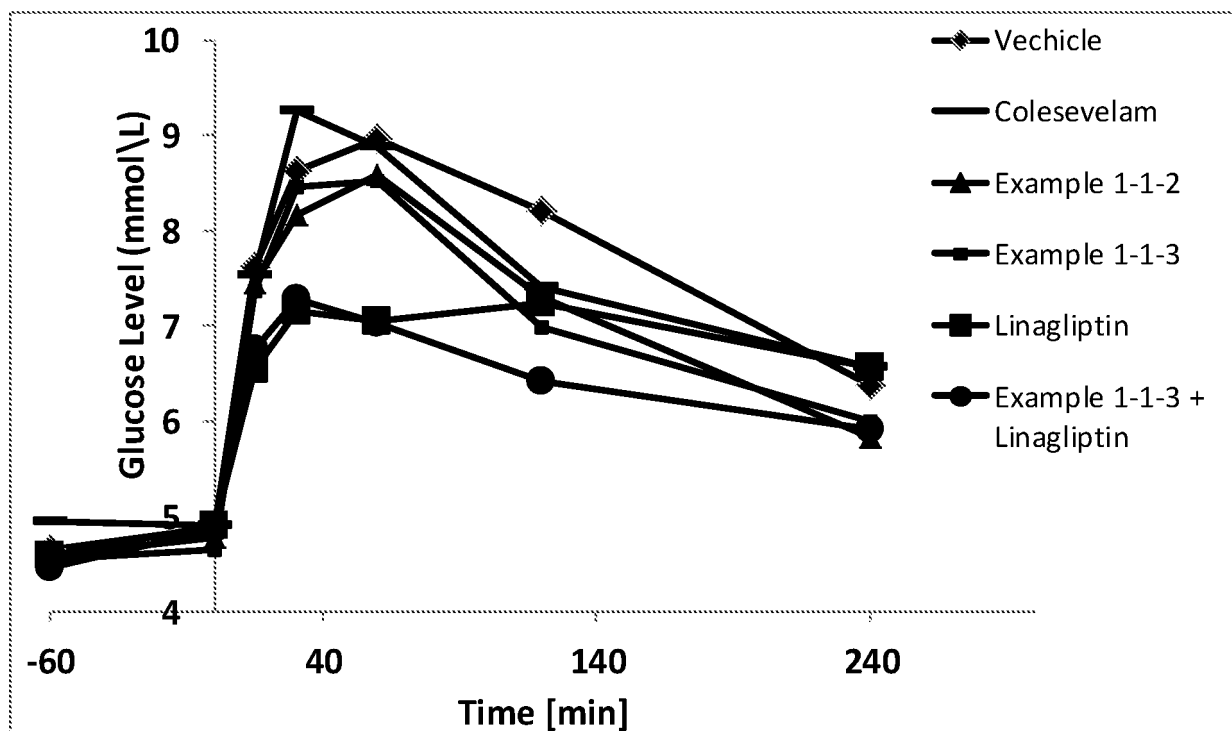
The effect of polydiallylamine copolymers on improving insulin resistance (glucose homeostasis) was evaluated by an oral glucose tolerance test (OGTT) using diet induced obese (DIO) rats as the disease models. Male SPD rats of seven week age (Taconic, Denmark) were given a diet consisting of normal chow and high fat content diet. After feeding with this diet for 24 weeks, the animals were randomized based on body weight and whole body fat. Each treatment group contains 10 animals. The animals were placed individually in separate cages throughout the study period. Subsequently the animals were given the above food mixed with appropriate amounts of the polymers in the food for four weeks. At the end of the fourth week, OGTT was carried out. For OGTT, after subjecting to fasting for 16 hours, the animals were administered dextrose (1 g/kg) by oral route. Blood samples were collected one hour and immediately before dextrose treatment as well as at specific time intervals up to 4 hr after dextrose treatment. Serum glucose levels in the blood samples. The average blood glucose concentration (AUC) during the entire time course for each treatment group is presented in Table 9.

Table 9: *In vivo* Effect on Blood Glucose with Crosslinked PDA-PVAm and PDA-PAA Copolymers

Test Article	Dose (% of diet)	[Blood Glucose]_{average} (mmol/L*min)[†]
Control	0	2154
Example 1-1-2	1.2	2005
Example 1-1-3	1.2	1982
Example 1-1-3+ Lingalipitin	1.2 + 3 mg/kg	1827
Colesevelam	1.2	2112
Linagliptin	3 mg/kg	1940

[†] Average blood glucose concentration from -60 minutes to +240 minutes, followed by oral glucose administration

Figure 9: *In vivo* Effect on Blood Glucose Profile with Crosslinked PDA-PVAm and PDA-PAA Copolymers



Example 3- 4: *In vivo* Anti-Diabetic Properties of Crosslinked PDA-PVAm and PDA-PAA Copolymers

Six week old obese, diabetic KKAY mice were housed in a temperature controlled room with a dark-light cycle of 12 hours each. One week after arrival at the animal facility, the animals were grouped as a group of 8. The animals were put on high fat diet for additional 3 weeks. When target level of blood glucose and HbA1c was achieved, the diet was supplemented with the polymers at different weight % of the diet. Animals were treated with polymer mixed diet for six weeks. The animals were monitored for body weights and food intake every other day. Fed and semi-fasted blood glucose, HbA1c, and plasma insulin were measured before start of the experiment and at the end of every week of treatment. The effect of treatment on blood glucose and HbA1c was measured and the results are summarized as difference in their values at the start of the study and at the end of seven weeks of treatment and presented in Figure 10 and Figure 11 below.

Figure 10: *In vivo* Effect on Blood Glucose of KKAY mice treated with Crosslinked PDA-PAA Copolymer after 7 Weeks of Treatment

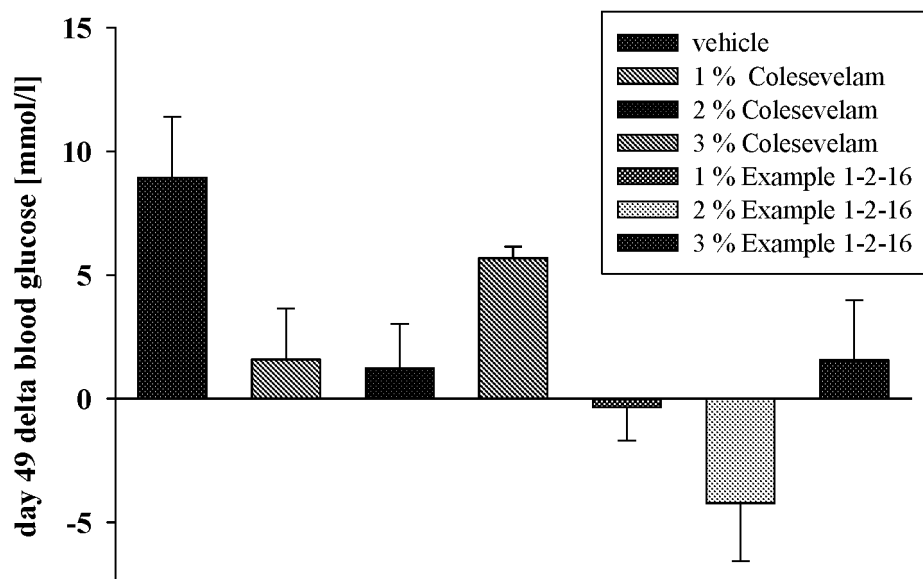


Figure 11: *In vivo* Effect on HbA1c of KKAY mice treated with Crosslinked PDA-PAA Copolymer after 7 Weeks of Treatment

